Institute of Diabetes "Gerhardt Katsch" Karlsburg
(IDK)

Report

Evaluation of system accuracy of the blood glucose monitoring system VivaChek™ Ino according to DIN EN ISO 15197: 2013

Sponsor:	VivaChek Laboratories, Inc. 913 N Market Street, Suite 200 Wilmington, DE 19081 USA
The study was conducted in:	Institute of Diabetes „Gerhardt Katsch" Karlsburg e.V. Greifswalder Straße 11 e 17495 Karlsburg
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1. Introduction

The aim of the modern diabetes therapy is the maintenance of near normal blood glucose concentrations to prevent both hypo- and hyperglycaemic excursions that have been closely associated with the development of acute and late complications of the disease.
Blood glucose monitoring/measurement systems, which can be used for self-determination of the blood glucose by the patient, are helpful for a better metabolic control by the patients themselves and by the physician and allow a more flexible adjustment of the individual medication/therapy.
To achieve this goal, any insulin dose adjustment should precede the blood glucose self control using blood glucose monitoring systems with a high quality and measurement accuracy.
The directive DIN EN ISO 15197 [1] demands strict international quality standards for the system accuracy of blood glucose monitoring systems (BGMS). The DIN EN ISO 15197:2013 [2] represents a revision of the DIN EN ISO 15197:2003 [1]. The minimal acceptable accuracy for measurements using BGMS is defined as follows:
For blood glucose concentrations <5.55 mmol/l (< 100 mg/dl) the glucose values are allowed to differ in comparison to the reference method up to ± 0.83 mmol/l (± 15 mg/dl).
In the case of blood glucose concentrations of ≥5.55 mmol/l (≥ 100 mg/dl) only deviations of less than 15% as compared to the reference method are acceptable.
In addition, the above criteria must be met by at least 95% of the measured values.
According to §23b MPG, the present study has tested the system accuracy in accordance to DIN EN ISO 15197:2013 for the system VivaChek™ Ino. The blood glucose monitoring system has already a CE-marking and meets the requirements of the directive 98/79/EG.

This protocol had been submitted as an amendment to the Independent Ethics Committee Greifswald before initiation of the study (Interne Reg. Nr.: BB 081/15).
The study has been announced to the Health Authority according to §20 MPG.
If systems without CE-marks are tested, the manufacturer/customer of the study must provide a Manufacturer's Declaration according to §12(3), §24(2) of the Medical Devices Act and Annex VIII of the Directive 98/79/EC of in vitro diagnostic medical devices of the European Parliament and of the Council of Oct. 27, 1998. This Manufacturer's Declaration will be submitted to the Health Authority in the context of an amendment.
The glucose monitoring system had a CE certification.
Volunteers were insured by an insurance agency.

2. Aim

The aim of this investigation was to proof the system accuracy of the VivaChek™ Ino in accordance with the directive DIN EN ISO 15197: 2013. Reference measurements were performed with the YSI 2300 STAT PLUS system.

3. Study design

Capillary blood, taken from the earlobe of patients (skin disinfection before puncture with a lancet), was used for the measurement of blood glucose concentration by the test- (VivaChek™ Ino) and reference method (YSI 2300).
The ethic vote for the study was given from the ethic committee of the University Greifswald on 4th of June 2015.

3.1 Test persons

The volunteers had to meet the following inclusion criteria:

- Male or female patients with hypo-, normo- or hyperglycaemia
- The written informed consent had to be signed.
- The volunteers must be older than 18 years.
- The volunteers have legal capacity and are able to understand meaning, nature and possible consequences.
- The subjects will receive 10.00 € for expenses.

The exclusion criteria:

- Pregnancy or lactation.
- Acute or chronic diseases with the risk of aggravation by the measure.
- A current constitution which does not allow participating in the study.

3.2. Study period

The blood withdrawal in a patient took 5 to 10 minutes.

3.3. Screening

To attract potential subjects for the study, peoples were first informed about the objective, procedure, risk and duration of the study. After declaration of willingness to participate in the study, written consent from the volunteer was requested. On the experimental day, good physical fitness was a prerequisite for blood sampling.

3.4. Risks of experimental procedure / termination criteria

The blood sampling was executed by qualified persons under strict hygienic conditions, using only disposable material to minimize the risks for the subjects. In case of discomfort of a subject, blood sampling was interrupted.

3.5. Material and methods

3.5.1. Test device

VivaChek™ Ino

Manufacturer: VivaChek Laboratories, Inc.
913 N Market Street, Suite 200
Wilmington, DE 19081, USA

Technical data:
Blood sample: Capillary blood
Sample volume: 0.5 µl
Glucose measurement range: 10 - 600 mg/dl
Measuring time: 5 sec
Working temperature: 5 - 45°C
Relative humidity: 10 - 90%
Hematocrit: 20 - 70%
Technology: Amperometric biosensor, enzyme type: GOD
Calibration: Plasma equivalent
Code: Autocoding

For the tests, three blood glucose monitors type VivaChek™ Ino were available and two of them used during the tests.

Serial number and study code of the provided VivaChek™ Ino monitors:

Serial number	**Study code**
10101A0005669	GC 1
10101A0005666	GC 2
10101A000569D	Not used to measure

Test strips
In total, 350 test strips from each of 3 lots were available. Reagent systems from 13 packs were used per lot. The following lots were included into the tests:

Test strips		
Numbering	**Lot No.**	**Expiration date**
Lot 1	1100080	2017/02
Lot 2	1100081	2017/02
Lot 3	1100082	2017/02

Control measurements
The control measurements were carried out using three control solutions, whose characteristics are listed in the following table:

Control solution	**Lot No.**	**Expiration date**	**Target area (mg/dl) of test strips** Lot 1	Lot 2	Lot 3
Level 1: GCS Low	AL20001	2017/04	29-59	30-60	28-59
Level 2: GCS Normal	AN20019	2017/04	94-141	95-142	93-140
Level 3: GCS High	AH20001	2017/04	275-414	277-416	274-415

The measurements were performed according to the instructions by the manufacturer. On each study day before the test measurements, control measurements in each range and for each test strip lot and each monitor were performed (Excel table “controls”).
The system was found to be appropriate when the control measurements fell into the range that has been specified by the manufacturer.
The results of the control measurements were within the desired range, so that no device had to be replaced.

3.5.2. Reference device

YSI 2300 STAT PLUS Manufacturer: YSI Incorporated, Yellow Springs, Ohio, USA
Method: Glucose Oxidase (GOD)
Probe: Lithium-Heparin-Plasma sampled from capillary blood
Duplicate = measurement with 2 electrodes
Sample volume: 25 µl
Glucose measurement range: up to 900 mg/dl (to 50 mmol/l)
Measuring time: 65 sec
Working temperature: 15 - 35°C
Relative humidity: 10 - 90%
Calibration: at 180 mg/dl

Accuracy and Precision
The proof of accuracy and precision was performed by use of YSI Standards with glucose concentrations of 90 mg/dl, 180 mg/dl, 450 mg/dl and 900 mg/dl, respectively. The standards were measured on the test day, before, during and after the test series.

Maintenance, adjustment and control procedures
For all the equipment used during the study, the control procedure has been implemented according to the manufacturer's instructions.

3.5.3. Determination of hematocrit
The procedure was performed in accordance with DIN 58933-1. The blood was sampled in heparinized micro-hematocrit capillaries (Laboratory Glassware, Marienfeld, Germany), which were closed and centrifuged thereafter (Hettich centrifuge HAEMATOKRIT 200; Germany). Reading the hematocrit value was performed by using a Nomogram.

4. Execution of the study in accordance with the requirements of DIN EN ISO 15197:2013

4.1. Samples
A total of 104 capillary blood samples were taken. After evaluation of glucose concentration ranges using the reference method YSI, exactly 100 samples were included into the stat.
To reach the lower blood glucose ranges < 80 mg/dl, the glucose concentration was decreased by storage of the samples at 37°C (stored).
To reach the higher blood glucose ranges, the Lithium-Heparin-blood (300 µl) was spiked with a 40% glucose solution (B. Braun, Melsungen, Deutschland) (spiked).
For the measurements of original blood samples (original), 300 µl blood were sampled from the earlobe into Lithium-Heparin tubes (Mikrovetten®, Sarstedt AG & Co., Nümbrecht, Germany). Thereafter, blood was divided into 2 aliquots, which were used for reference measurements (YSI) after plasma separation before and after test strip measurements. The first reference sample was analysed directly after the sampling procedure and the second directly after the test strip measurements. In accordance with the requirements as described in DIN EN ISO 15197:2013, samples of the following concentration ranges were included into the procedure:

Range	Percentage of samples (%)	Glucose concentration(mg/dl)	Sample handling
1	5	≤50	all stored
2	15	> 50 - 80	9 unchanged and 6 stored
3	20	> 80 - 120	all unchanged
4	30	> 120 - 200	all unchanged
5	15	> 200 - 300	all unchanged
6	10	> 300 - 400	8 unchanged and 2 spiked
7	5	> 400	all spiked

The assignment to the concentration ranges based on the results of the reference measurements that have been done using the YSI 2300 STAT PLUS.

4.2. Blood glucose monitoring systems

Before start of the study, medical technical personnel were instructed in correct handling of the measuring systems. The devices had been properly maintained. Strips of each test lot were measured on two different devices.

4.3. Environmental conditions in the laboratory

During the study, room temperature ranged between 19.8°C und 25.3°C and the humidity between 42% to 54% (Excel table "conditions during the test"). So the prescribed external conditions were met for the blood glucose measurement systems (see characteristic of the test and reference device).

4.4. Additional exclusion criteria

The glucose concentration ranges were covered in accordance with the ranges in the table (see 4.1.) and unsuited blood samples (n=4) were excluded. Criterion for the exclusion was a difference of more than 4% between reference value 1 and 2, a failure during the measurement was documented, or the range of measurements was already completed.
The hematocrit of the samples should range between 20% und 70 % (a set in the manual of the manufacturer), which was observed in all samples. Accordingly, there was no reason to exclude blood samples due to hematocrit abnormalities. Only those data were included if the coefficient of variation of the duplicates - determined using the reference method – was below 4 %.

4.5. Determination of glucose concentration using test strips

For use of original unchanged blood samples, capillary blood was taken directly from the earlobe to get contact to the test strip.
For reference measurements, blood was sampled into Lithium Heparin tubes (Mikrovetten®, 300 µl were divided into 150 µl aliquots). Plasma was separated for reference measurements using the YSI apparatus.

Sampling was performed in the following order:

1. 300 µl blood were taken from the earlobe into Lithium Heparin tubes for reference measurement (samples were divided into aliquots of 150 µl each). The first reference sample (R1) was analysed directly after sampling.
2. BGM measurements:
   - VivaChek™ Ino – GC 1 Lot 1
   - VivaChek™ Ino – GC 2 Lot 1
   - VivaChek™ Ino – GC 1 Lot 2
   - VivaChek™ Ino – GC 2 Lot 2
   - VivaChek™ Ino – GC 1 Lot 3
   - VivaChek™ Ino – GC 2 Lot 3
3. Analysis of the second reference sample (R2) using the reference method (YSI)
4. Blood sampling for determination of the hematocrit.

To get samples in the different by ISO defined ranges, the glucose concentration of any taken samples was adjusted in accordance with the instructions of DIN EN ISO 15197:2013 (blood spiked or blood stored). The spiked blood samples were safety mixed by rotation for 30 minutes at room temperature. Thereafter, an aliquot was taken for YSI reference measurements before and after BGM testing.

To get glucose concentrations < 80 mg/dl, blood samples were incubated at 37°C in a shaking water bath for 1 – 3 hours (stored) to be measured thereafter similar to the spiked samples.

5. Analysis / Results

5.1. Time of realization

The study was performed between June 30th and 17th of July 2015.

5.2. Data

A total of 100 patient sample data which fulfilled the inclusion criteria, were included in the statistical analysis.
Another 4 data sets had to be excluded (shown in 4.4.).
The complete data sets of the study are given in the Excel tables.

5.3. Analysis of system accuracy in accordance with DIN EN ISO 15197:2013 [1]

The analysis of data for the proof of system accuracy was done in accordance with the instructions given in the DIN EN ISO 15197:2013 [1]. The test measurements were compared with the reference values determined using the YSI 2300 STAT PLUS system.
For samples with concentrations <100 mg/dl the deviation of test values from the mean of the reference values were calculated in mg/dl. For samples with glucose concentrations >100 mg/dl the percentage deviation form the mean of the reference values were calculated.

The following parameters were calculated:

Drift in %	deviation of the reference values from YSI values in %
YSI average	mean of reference values in mg/dl
Dev. GC to YSI in mg/dl	average deviation of the measured values to the reference value in mg/dl
Dev. GC to YSI in %	average deviation of the measured values to the reference value in %

Result of system accuracy of VivaChek™ Ino for glucose concentrations <100 mg/dL

	within ± 5mg/dL	**within ± 10mg/dL**	**within ± 15mg/dL**
Lot 1 (1100080)	26/62 (41.9%)	55/62 (88.7%)	62/62 (100%)
Lot 2 (1100081)	29/62 (46.8%)	53/62 (85.5%)	62/62 (100%)
Lot 3 (1100082)	23/62 (37.1%)	40/62 (64.5%)	61/62 (98.4%)
Lot 1, 2 and 3 in summary	78/186 (41.9%)	148/186 (79.6%)	185/186 (99.5%)

Result of system accuracy of VivaChek™ Ino for glucose concentrations >100 mg/dL

	within ± 5%	within ± 10%	within ± 15%
Lot 1 (1100080)	79/138 (57.3%)	121/138 (87.7%)	136/138 (98.6%)
Lot 2 (1100081)	74/138 (53.6%)	121/138 (87.7%)	136/138 (98.6%)
Lot 3 (1100082)	80/138 (58.0%)	118/138 (85.5%)	136/138 (98.6%)
Lot 1, 2 and 3 in summary	233/414 (56.3%)	360/414 (87.0%)	408/414 (98.6%)

System accuracy of VivaChek™ Ino for combined glucose concentrations

	within ± 15 mg/dL or 15%
Lot 1 (1100080)	198/200 (99.0%)
Lot 2 (1100081)	198/200 (99.0%)
Lot 3 (1100082)	197/200 (98.5%)
Lot 1, 2 and 3 in summary	593/600 (98.8%)

In all three test strip lots more than 95% of the readings had a deviation to the reference method of less than 15% (for values > 100 mg/dl) or of less than 15 mg/dl (for values < 100 mg/dl) respectively.

A regression analysis was performed according to Passing and Bablok [4] and the readings are shown in the Error Grid Diagram.

Figure 1: Error Grid Analysis of test Lot 1 (1100080),
Mean values of VivaChek™ Ino vs. mean values of the YSI 2300 Stat Plus

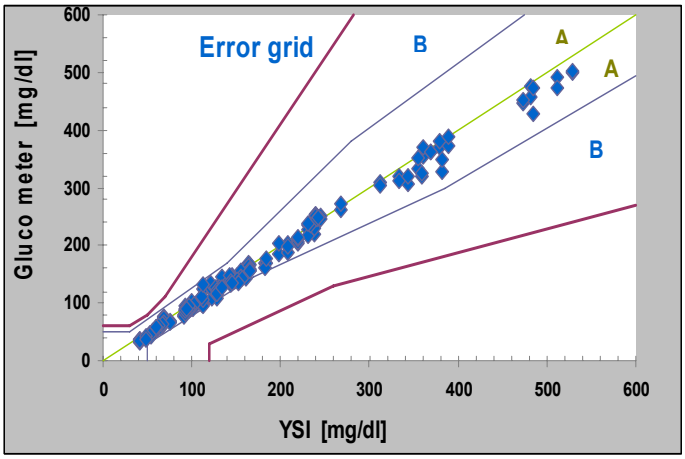


Figure 2: Graphic representation of the differences between the VivaChek™ Ino (Lot 1) and reference measurements, as a function of the glucose concentration

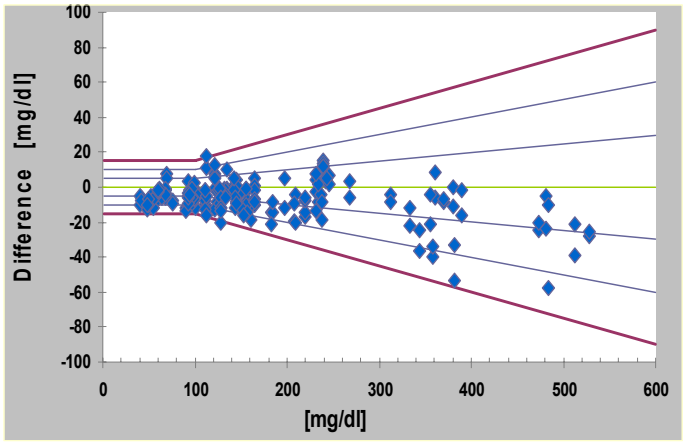


Figure 3: Error Grid Analysis of test Lot 2 (1100081),
Mean values of VivaChek™ Ino vs. mean values of the YSI 2300 Stat Plus

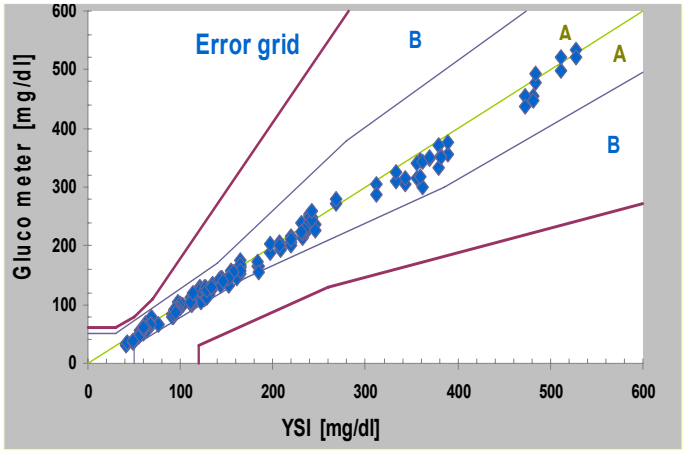


Figure 4: Graphic representation of the differences between the VivaChek™ Ino (Lot 2) and reference measurements, as a function of the glucose concentration

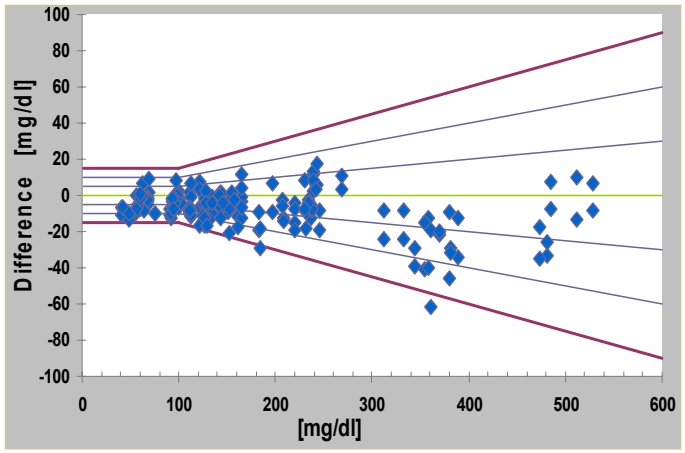


Figure 5: Error Grid Analysis of test Lot 3 (1100082),
Mean values of VivaChek™ Ino vs. mean values of the YSI 2300 Stat Plus

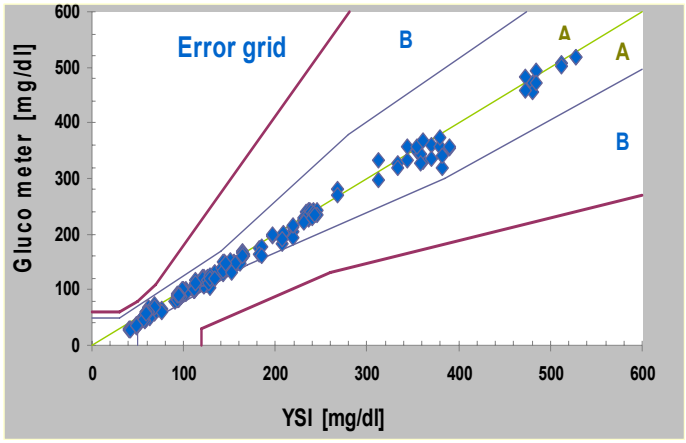
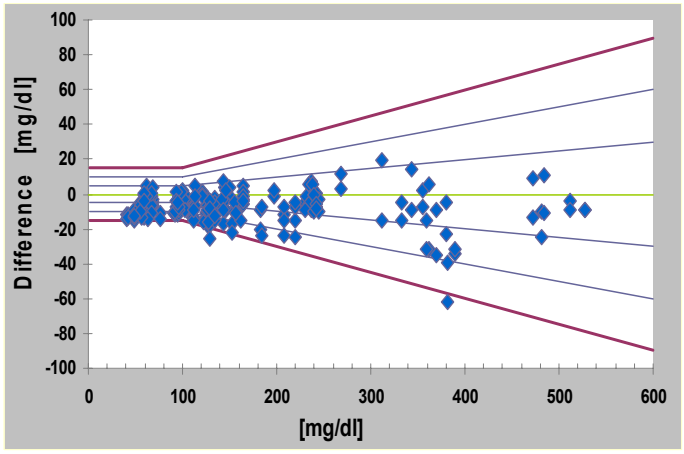


Figure 6: Graphic representation of the differences between the VivaChek™ Ino (Lot 3) and reference measurements, as a function of the glucose concentration



The readings of all three test lots were within the region A and B of the Parkes Error Grid.

6. Summary and conclusions

The criteria for the system accuracy according to the Norm DIN EN ISO 15197:2013 were fulfilled for the blood glucose monitoring system VivaChek™ Ino.

- 100% of the performed measurements were within the zone A and B of the Consensus Error Grid [5].
- According to the results of system accuracy 98.8% of all measurements were within the required range.
- For the VivaChek™ Ino system, the criteria of the DIN EN ISO 15197:2013 were met by the study data.

References

1. Testsysteme für die In-vitro-Diagnostik – Anforderungen an Blutzuckermesssysteme zur Eigenanwendung beim Diabetes mellitus (DIN EN ISO 15197:2003)

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3. Bland J.M. and Altman D.G.: Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986, 307-310.

4. Passing H. and Bablok W.: A new biometrical procedure for testing the equality of measurements from two different analytical methods. J Clin Chem Clin Biochem Vol. 21, 1983: 709-720.

5. Parkes J.L., Slatin S.L., Pardo S., Ginsberg B.H.: A New Consensus Error Grid to Evaluate the Clinical Significance of Inaccuracies in the Measurement of Blood Glucose. Diabetes Care 2000. 23:1143–1148.

Signatures

The undersigned has reviewed the format and content of this report.

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